REMARKS

Claims 1-5, 10-17, 23-26, and 29-39 are pending in this application, and claims 25, 26, 38, and 39 are withdrawn from consideration. With this response, Applicants amend claims 1, 3-5, 23, 38, and 39, and cancel claims 36 and 37. Support for the amendment to the claims can be found throughout the specification, for example, at page 5, ¶ 15; page 12, ¶ 37; page 13, ¶ 40, and in the Examples, specifically at Examples 5-12. No new matter is added by this amendment.

Applicants also include amendment to the specification in order to correct a typographical error. No new matter is added by virtue of this amendment, and its entry is respectfully requested.

Claim Objections

Claims 1, and 12-17 are objected to because they recite the acronyms "GDF-8," and "ActRIIB," which the Examiner alleges should be spelled out in all independent claims.

Applicants have amended claim 1 as suggested by the Examiner, thus rendering this objection moot.

Claim Rejections - 35 U.S.C. § 112

The Examiner rejects claims 1-5, 10-17, 23, and 29-37 as allegedly lacking enablement and written description under 35 U.S.C. § 112, first paragraph. The Examiner further rejects claims 1-5, 10-17, 23, and 29-37 under 35 U.S.C. § 112, second paragraph as allegedly indefinite.

A. Enablement

The Examiner rejects claims 1-5, 10-17, 23, and 29-37 as allegedly lacking enablement, and contends that while the specification is enabling for stimulation of increased muscle mass via administration of the ActRIIB-Fc fusion polypeptide exemplified in Example 9, it does not enable a method for ameliorating any symptom of a degenerative disorder of muscle by administering a polypeptide that is at least 95% to 99% identical to the exemplified ActRIIB-Fc fusion polypeptide.

Applicants respectfully disagree that the claims are not enabled for method for ameliorating symptoms of GDF-8-related diseases and disorders. However, to expedite prosecution and place all claims in condition for immediate allowance, Applicants have amended the claims to recite a method for increasing muscle mass in an individual with a disease or disorder in which an increase in muscle mass is desirable.

The Examiner further alleges that the specification is not enabling because it does not teach which residues of the claimed polypeptide can be modified such that the protein maintains functionality, further arguing that there is no physiological activity associated with these variants. Applicants respectfully disagree. The claims are directed to methods for increasing muscle mass by administering an ActRIIB-Fc fusion polypeptide that comprises an amino acid sequence that is at least 95% to 99% identical to amino acids 23 to 138 of SEQ ID NO:3. The claims also specify that the polypeptide bind to GDF-8, and inhibit a GDF-8 activity associated with negative regulation of muscle mass, modulation of muscle-specific enzymes, stimulation of myoblast proliferation, or modulation of preadipocyte differentiation to adipocytes.

Applicants respectfully submit that the law does not require an application to teach what is already known or readily discernable to those of skill in the relevant art. The test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976). The skilled artisan need not be able to predict in advance which modifications will result in a protein that retains function. Trial and error experimentation will readily provide this information. As noted by the Federal Circuit, trial and error experimentation is not necessarily undue. See, e.g., In re Wands, 858 F.2d 731 (Fed. Cir. 1988) (concluding that screening many hybridomas to find the few that fell within the claims was not undue experimentation).

In the instant case, the claims are enabled because the specification and knowledge in the art provide ample guidance as to changes that could be made to the polypeptide sequences without disrupting its GDF-8 binding activity. In addition, any experimentation that would need to be done to confirm the GDF-8 binding activity of a modified protein would not be undue. In fact, guidelines for producing variants likely to retain GDF-8 binding activity were known to those of skill in the art and are referenced, for example, at page 17, ¶ 51, and are specifically exemplified at Examples 5-6.

Furthermore, a polypeptide that falls within the scope of the claims has physical properties, and functional characteristics that are easily determined by one of skill in the art. For example, in one embodiment, the polypeptide must comprise a sequence that is at least 95% identical to amino acids 23-138 of SEQ ID NO:3. Determining which proteins have this property simply requires sequencing the encoding DNA or the protein itself, both of which are routine tasks. The claims also specify the functional limitation

that the polypeptide inhibits a GDF-8 activity. GDF-8 activity assays are routine and well within the knowledge of those with skill in the art. Furthermore, the specification teaches how to perform such assays, for example, at Examples 6 (*in vitro*), and 8-12 (*in vivo*).

Accordingly, based on the disclosure in the specification, and the knowledge of those skilled in the art at the time of filing, the experimentation involved in selecting a polypeptide with 95% to 99% identity to amino acids 23-138 of SEQ ID NO:3 (which at most includes 5 amino acid differences) that maintains its ability to bind to GDF-8, and inhibits a GDF-8 activity when altered does not rise to the level of "undue experimentation", as analyzed under the factors of In re Wands, 858 F.2d 731 (Fed. Cir. 1988).

B. Written Description

The Examiner rejects claims 1-5, 10-17, 23, and 29-37 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that is not described in the specification in such a manner as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner contends that the specification does not adequately support the claimed ActRIIB fusion polypeptides, and specifically states that the specification does not provide guidance on how to make an ActRIIB-Fc polypeptide with 1% to 5% sequence variability. The Examiner further argues that "binding to GDF-8" does not adequately describe the functional characteristics of such polypeptides (see Office Action, page 10).

Applicants respectfully disagree that claims reciting polypeptides with up to 5% sequence difference from a specified sequence are not adequately described. Applicants' support for the polypeptide described in amended claims 1-5, 10-17, 23, and 29-37 exceeds the written description standard articulated by the PTO's Written Description Guidelines. Example 14 of the Written Description Guidelines states that disclosure of a single protein sequence provides adequate written description support for the genus of proteins comprising sequences that are at least 95% identical to that sequence and catalyze the reaction of A to B.

As in Example 14, the rejected claims relate to a protein (an ActRIIB fusion polypeptide) comprising an amino acid sequence that satisfies a functional limitation (having GDF-8 binding activity, and inhibiting a GDF-8 activity associated with negative regulation of muscle mass, modulation of muscle-specific enzymes, stimulation of myoblast proliferation, and modulation of preadipocyte differentiation to adipocytes) and a structural limitation (having a sequence at least 95% identical to amino acids 23-138 of SEQ ID NO:3). As in Example 14, the specification and knowledge in the art provide procedures for making variants of the disclosed sequence and assays to identify variants satisfying the functional limitation (as described in more detail below).

The Federal Circuit has stated that an adequate written description of a DNA or protein "requires a precise definition, such as by structure, formula, chemical name, or physical properties." Fiers v. Revel, 984 F.2d 1164, 1171 (Fed. Cir. 1993)(emphasis added). The specification of the instant invention provides both structural guidance and physical properties for the claimed genus. For example, as discussed above, the rejected claims share the structural feature of having at least 95% identity to amino

acids 23-138 of SEQ ID NO:3, and the physical property of being capable of binding to GDF-8, and inhibiting a GDF-8 associated activity. One with skill in the relevant art would know how to identify such members of the genus based on structure, which is provided in the specification at SEQ ID NO:3, or based on an analysis of the physical properties, which is provided throughout the specification, particularly at the Examples. For example, the specification provides simple and routine assays for determining whether any given ActRIIB polypeptide or ActRIIB polypeptide variant binds to GDF-8 (see Example 5). Furthermore, simple and routine assays for determining whether any given ActRIIB polypeptide or polypeptide variant reduces a GDF-8 activity are also described in the specification and are known to those of skill in the art (see page 19, ¶ 54; and Examples 6-10). Nothing more is necessary to meet the written description requirement of 35 U.S.C. § 112, first paragraph.

C. Indefiniteness

Claims 1-5, 10-17, 23, and 29-37 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

The Examiner alleges that the term "stringent" in claim 23 is vague. Without acquiescing, Applicants amend claim 23 to provide hybridization conditions. Support for this amendment can be found in the specification on page 13, ¶ 40.

The Examiner further alleges that the term "GDF-8 activity" in claims 1-5, 10-17, 23, and 29-37 is a relative term which renders the claim indefinite. Without acquiescing, Applicants amend independent claim 1 to state that the GDF-8 activity is chosen from negative regulation of skeletal muscle mass, modulation of muscle-specific enzymes, stimulation of myoblast proliferation, and modulation of preadipocyte differentiation to

adipocytes. Support for this amendment can be found at page 12, ¶ 37; and page 5, ¶ 13.

Accordingly, Applicants respectfully ask the Examiner to withdraw the rejections to the claims under 35 U.S.C. § 112, second paragraph.

Conclusions

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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